Application Content

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IV. Device Characteristics and Manufacturing Section

A. Description

Provide a detailed description of the replacement heart valve. Discuss the engineering considerations that went into the design specifications. Photographs of each type (aortic and/or mitral) in both the fully opened and fully closed position must be submitted. Drawings, including dimensional specifications for each tissue annulus diameter, must be included.

B. Description of each of the components

Provide a complete listing of all materials used in the fabrication or processing of the replacement heart valve. Include the generic chemical name or biological source. Indicate the thermal/mechanical/chemical condition of all constituent materials in both the raw material and finished product form (e.g., for metals: cast, solution annealed, percent cold worked, etc.; for polymers: degree of crystallinity, molecular weight distribution, etc.; for ceramics: degree of crystallinity, etc.).

Characterize all materials in the condition they are used in the finished product. The following characteristics and their allowable tolerances shall be included, as applicable for each material: density, composition, elastic modulus, shear modulus, tensile strength, yield strength, flexural strength, strain to failure, hardness, corrosion resistance, abrasion resistance, creep at maximum design load. Pyrolytic carbon, which is used in many mechanical heart valves, is the only ceramic material currently used to manufacture prosthetic heart valves in the United States. [Note: the use of the word ceramic here is intended to imply any non-metallic, inorganic, low toughness material which does not show (metal-like) plasticity at room temperature]. The materials characterization section of appendix B contains an indication of the specific types of information which must be included for pyrolytic carbon.

C. Description of the properties relevant to treatment

The rationale used to establish and optimize key design features of the valve, including but not limited to hemodynamic function, occluder geometry and kinematics, choice of materials, and structural configuration. For mechanical valves, this description must also include a discussion of opening angle. For tilting disc valves, information on the optimization of disc curvature and eccentricity (the ratio of the displacement of the pivot axis from the valve center to the occluder diameter) may be appropriate. This discussion should focus on the fact that literature reports have shown that optimizing the quantities is essential in controlling the opening torque, flutter, pressure losses across the valve, and flow characteristics.

D. Description of the principles of operation

A discussion of the effect of time on the pressures in the chambers of the heart and the aorta, and how the pressure differences which result due to these changes, produce valve opening and closing.

E. Manufacturing Information

Recently the Office of Compliance (OC) and ODE have established a formal agreement on the review of manufacturing information in original PMAs, as well as certain select supplements to the PMA. It is part of an agency-wide initiative to improve the premarket assessment of new products. Under this program, which is known as the "Medical Device Premarket Approval Inspections," manufacturing information submitted with a PMA will be forwarded to OC to determine the extent to which the application contains sufficient information for an evaluation of the sponsor's capability to manufacture the device.

The implementation of Compliance Program 7383.001 directs the field to consider the extent to which the firm has established a formal quality assurance program and has assured that the approved design is properly translated into specifications via process validation. Manufacturers are referred to the following documents to obtain specific information on the manufacturing information which must be submitted: "Guideline on General Principles of Process Validation," "PMA Compliance Program" (Blue Book PMA Memorandum #P91-3), and "Guidance for Preparation of PMA Manufacturing Information." Please note that the information on manufacturing which is included in the PMA Approval Manual (FDA 87-4214) is obsolete.

Although the "Guidance for Preparation of PMA Manufacturing Applications" applies to all devices which undergo PMA review, there are several issues which ODE feels are particularly critical in the manufacturing of replacement heart valves. In particular, then, DCRND suggests that in addition to that information which is noted in the OC guidance, the following information must be incorporated into the appropriate areas of the manufacturing section:

1. Manufacturing

(i) For mechanical valves, details of the procedure used to insert the occluder and/or leaflets into place must be provided; (ii) A detailed validation study of the manufacturing process must be conducted, and the results presented. Appendix B addresses process validation requirements for pyrolytic carbon.

2. Processing

(i) For tissue valves, tissue fixation parameters, and acceptance criteria for valves as received from the slaughter house must be described. These acceptance criteria must include not only the maximum allowable size for fenestrations, tears, and tissue peel, but also a maximum allowable number of defects per valve, as well as critical locations which must not contain defects.

3. Packaging

(i) Details of the unit container design must be included, focusing on the feature which indicates if the package has been opened; (ii) For tissue valves, the use of a temperature sensor is highly recommended, and information on the validation of the sensitivity of the sensor must be included.

4. Sterilization

(i) It is the opinion of FDA that replacement heart valves should be supplied sterile. Therefore, a justification for distributing non-sterile devices should be included, if it is the intention of the manufacturer to do so; (ii) The results of a validation study which shows that the sterilization process provides a sterility assurance level (SAL) of at least 10^{-6}, i.e. the probability of finding an unsterile device is one in one million, must be provided. There are numerous voluntary standards available that address the issue of sterilization validation. Manufacturers should refer to ISO 11134 and 11135. The validation must include use of inoculated product or indicators (biological or other types) placed in the most difficult location of the device, and within the sterilization chamber. Viable spore count on biological indicators must be verified prior to each use. The organism chosen as the indicator must represent the worst case organism for the particular type of sterilization method chosen. All equipment used during the process to monitor conditions (thermocouples, gages, etc.) must have been recently calibrated. It must be demonstrated that the methods chosen are be compatible with the device and packaging materials; (iii) Supply information on the controls that are present to ensure that the bioburden on the device is low. e.g., the cleaning schedule for the floors and other surfaces, disinfection procedures, management of water and systems, laminar flow hoods, sterilizers, etc. The warning and action limits for bioburden must be specified.

5. Resterilization

(i) If resterilization is allowed, a justification for allowing such must be provided; (ii) Furthermore, a description which differentiates between those sterilizations conducted at the manufacturing facility and those performed by hospital staff must be furnished; (iii) A validation of the effect of resterilization on the valve must be included. The data must demonstrate that subjecting the valve to the maximum recommended number of resterilizations does not adversely affect the safety and effectiveness of the valve. The _in vitro_ tests which will adequately establish that degradation of the valve has not occurred are dependent on the type of valve (mechanical or tissue); the choice of tests is left to the discretion of the manufacturer. Testing of the package is to include an assessment of package integrity (via use of a microbial challenge followed by sterility assessment of the contents).

6. Storage

(i) Supply a list of the storage solution(s) for tissue valves. The manufacturer must use the rinse solution procedure specified in the labeling, then determine the residual storage solution levels in both the valve tissue and the rinse solution.

7. Labeling

All labeling must be in accordance with 21 CFR 801. Replacement heart valves are prescription devices; therefore the specific requirements are identified in 21 CFR 801.109. The following sources should be consulted for the CDRH interpretation of this regulation: _Labeling, Regulatory Requirements for Medical Devices_ (FDA 89-4203); ODE Guidance Memorandum (Blue Book) "Device Labeling Guidance", which is located in _Premarket Approval Manual Supplement_ (FDA 91-4245). These documents apply to all devices, however, the following specific information must be included for replacement heart valves, or a justification for not including it must be provided.

The instructions for use should contain the following information:
(i) Description, including the various types of the valves which are to be marketed, alternate sewing ring materials, and

alternate sewing ring configurations. Also, the location of the radiopaque marker, if present, must be described;
(ii) Specifications for each tissue annulus diameter;
(iii) Indications for use;
(iv) Contraindications (as appropriate for study design): for mechanical heart valves, the valve should not be implanted in patients who can not tolerate long-term anticoagulation therapy; for high profile valves, the valve should not be implanted if the patient's aortic root is too small (for aortic valves) or the left ventricle is too small (for mitral valves); for tissue valves, where appropriate, the valves should not be implanted in children, or patients with abnormal calcium metabolism, or those who are undergoing chronic hemodialysis;
(v) Warnings and Precautions (as appropriate for study design): valves are for single patient use only; prophylactic antibiotic treatment must be provided to all patients undergoing dental procedures, or in any potentially bacteremic situations; mechanical valves must not be crossed with a catheter, as damage to the valve may occur; for valves made from pyrolytic carbon, scratching the surface may lead to a loss of structural integrity; for mechanical valves which can be rotated, freedom of rotation must be established before implanting; the importance of appropriate sizing, including the clinical sequela associated with over and under-sizing; the requirement for (but not specification of) anticoagulation, both short and long term, as appropriate; for tissue valves, where appropriate, directions to avoid exposure to antibiotics, and to keep the valve moist during the implant operation, effects of nuclear magnetic resonance imaging;
(vi) Sterile and non-pyrogenic if seal and package are not opened, damaged, or broken;
(vii) Insertion orientation;
(viii) Summary of clinical experience used to support the approval of the device including: number of patients, type of implants, follow-up periods, post-operative complication rates, hemodynamic data, blood data, and improvements in NYHA classification.
(ix) A description of how the valve is packaged and supplied (sterile, storage solution, etc);
(x) Recommended storage conditions;
(xi) For tissue valves, recommended practices for rinsing the storage solution. Specify the volume and type of rinse solution
(xii) A description of patient ID cards, registration forms, etc.;to be used to adequately remove the storage solution;
(xiii) Description of the accessories;
(xiv) Date of latest revision;
(xv) If the labeling indicates that the replacement heart valve may be resterilized, recommended methods for resterilization, including sterilization parameters and a maximum allowable number of sterilizations. If a valve can not be resterilized, than include a statement to that effect;
(xvi) General surgical techniques, including some description of sizing techniques, general description of the preparation of the

implantation bed, and debridement of the area. Describe the importance of eliminating long suture ends, which could abrade tissue valves, or the importance of establishing leaflet/occluder mobility.

The unit container labeling should contain the following:
(i) Trade name;
(ii) Model, tissue annulus diameter and type of valve;
(iii) name and address of manufacturer;
(iv) batch code (lot or serial number);
(v) expiration data.

8. Sizing of the valve

The sizing method used in the manufacturing process must be described in detail. The sizing of a stented tissue or a mechanical valve is variable, but in general the tissue annulus diameter is defined as shown in Figure 1. The tissue annulus diameter of the stentless prosthesis is defined as the outer diameter at the inflow edge of the prosthesis. Figure 2 indicates the location used for sizing.

Regardless of the valve type, the measurement technique must not distort or stretch the prosthesis. A suggested method for assigning a tissue annulus diameter to stentless heart valves is provided in appendix C.

Manufacturers should be aware that the ODE and OC reviews of the manufacturing information are independent. The OC review focuses on 21 CFR Part 820 (Good Manufacturing Practice for Medical Devices: General), and the ODE review focuses on device-specific clinical and engineering issues.

V. Special Controls

Not applicable to class III devices.

VI. Technical Sections

A. Non-clinical laboratory studies

For each test in this section, a statement indicating whether the study was conducted in compliance with Good Laboratory Practice for Nonclinical Laboratory Studies, Part 58 must be included. If not, give a brief statement of the reason(s) for noncompliance.

1. Biocompatibility, Immunology, and Toxicology Issues

(i) Manufacturers should refer to International Standards Organization (ISO) 10993 (1993), Biological Evaluation of Medical Devices-Part 1: Guidance on selection of tests. (ii)

Pyrogenicity must be checked by limulus amebocyte lysate (LAL) methods of sufficient sensitivity or by using only rabbits previously tested for sensitivity to pyrogens. FDA requires that the endotoxin level not exceed 0.5 endotoxin units (EU) per ml. This testing must be done in no more than 40 ml of non-pyrogenic water. Additional information is available in "Guideline on Validation of the Limulus Amebocyte Lysate test for Human and Animal Parenteral Drugs, Biological Products, and Medical Devices;" (iii) The extraction conditions chosen for each biocompatibility test must be justified; (iv) If one or more of the recommended tests is not conducted, an adequate justification for each test not performed must be included; (v) Biocompatibility tests must be performed on the finished device, which has been sterilized the maximum recommended number of times, and if a rinse procedure is recommended in the labeling, the device must be rinsed prior to testing.

2. <u>In vitro</u> Studies

All <u>in vitro</u> testing must be performed on valves which are produced using the final design and manufacturing specifications. Test samples must be sterilized by the process to be used for production purposes. Furthermore, before conducting <u>in vitro</u> testing, the valve must be subjected to the maximum recommended number of resterilization cycles using the worst-case method and/or conditions specified for use with the valve. If necessary, removal of the sewing ring prior to testing is acceptable.

For those tests which call for the concurrent testing of a reference valve, the reference valve must be a model currently approved for marketing in the United States. With the exception of the cavitation testing, the reference valve must be the same type, and the designs should be similar. Therefore, a bileaflet valve should serve as a reference for a bileaflet, etc. For a stented tissue valve, the reference valve should be a stented tissue valve. Where possible, pericardial valves should be used as reference valves for pericardial valves, and porcine valves should be used as reference valves for porcine valves. The reference valve for a stentless prosthesis should be a stented porcine valve (until a stentless valve is cleared for marketing). Reference valves for all implant positions (aortic and mitral) for which the valve will be marketed must be tested.

As a general guide, the test report for each test must include the following:

- Rationale for the test;
- Number of samples tested and the serial numbers of the samples;
- Reference valve identification (where applicable);
- Test method employed. If an American Society for Testing and Materials (ASTM), Association for the Advancement of

Medical Instrumentation (AAMI), or an ISO standard is utilized, only the appropriate test number need be provided. If any other method is utilized (including internally generated test procedures), full details of the procedure must be included. Appendix D contains a listing of standardized test methods which may be applicable;

- Description of the apparatus. This must include all essential diagrams, measurement instrumentation specifications (including all pertinent information on the sensitivity of the equipment), representative pressure and flow waveforms (where applicable), and calibration techniques. Appendix E describes the recommended test chambers for hydrodynamic testing;
- Test chamber verification (for hydrodynamic testing) as described in Appendix F.
- Description of the test fluid, in accordance with the requirements given in Appendix G.
- Test data as required. For the purposes of providing the requested data, average refers to the arithmetic mean of all the samples of a particular tissue annulus diameter tested under identical conditions (e.g., the three size 19 mm aortic valves tested in the steady flow chamber at 5 l/min to determine pressure drop), and mean refers to the time-averaged arithmetic mean during one cycle;

a. Hydrodynamic performance

(1) Steady forward flow testing

Provide pressure drop, (ΔP), as a function of flow rate, (Q). Equipment and test apparatus must conform to ISO 5840. For mechanical and stented bioprosthetic valves, three valves of each tissue annulus diameter and one aortic (any tissue annulus diameter) and one mitral (any tissue annulus diameter) reference valve must be tested under identical conditions. In place of a reference valve, the system can be characterized using a standardized nozzle, as shown in appendix E. For stentless tissue valves, the testing must include three stentless valves of each tissue annulus diameter, one 19 mm, and one 31 mm aortic reference valve. For mechanical and stented tissue valves, the testing shall be conducted in an aortic or mitral flow chamber, as shown in appendix E. For stentless heart valves, the tests shall be conducted in a flow apparatus with 4% compliant chambers, unless the device is an intact root and it has been shown that device compliance is dominant, as outlined in appendix E, exclusion for intact root. Upstream ventricular pressure measurements must not exceed 200 mmHg.

Five equidistant flow rates will be used to adequately describe the relationship between pressure drop and flow rate over the range of 5 to 30 l/min. Data must be presented as follows: (i) table of pressure drop (mmHg), including the average and the standard deviation, and flow rate (l/min) for each tissue annulus diameter and type tested; (ii) one graph for each type of valve which shows pressure drop (mmHg) as a function of flow rate (l/min). See figure 3 for an example. The test report must contain the information designated in ISO 5840.

(2) Steady backflow leakage testing

Provide leakage rate as a function of back pressure. Equipment and test apparatus must conform to ISO 5840. For mechanical and stented bioprosthetic valves, three valves of each tissue annulus diameter and one aortic (any tissue annulus diameter) and one mitral (any tissue annulus diameter) reference valve must be tested under identical conditions. In place of a reference valve, the system can be characterized using a standardized nozzle, as shown in appendix E. For stentless tissue valves, the testing must include three stentless valves of each tissue annulus diameter, one 19 mm, and one 31 mm aortic reference valve. For mechanical and stented tissue valves, the testing shall be conducted in an aortic or mitral flow chamber, as shown in appendix E. For stentless heart valves, the tests shall be conducted in a flow apparatus with 4% and 16% compliant chambers, unless the device is an intact root prosthesis <u>and</u> it has been shown that device compliance is dominant, as outlined in appendix E, exclusion for intact root. Complete testing of stentless valves in 16% chambers is not required if data can be provided that shows that valve performance is not a function of chamber compliance, as outlined in appendix E, compliant aortic chamber, <u>compliance effect validation.</u>

For all valves, leakage rates must be measured for 5 equidistant back pressure differences over the range 40 to 190 mmHg. Data must be presented as follows: (i) table of leakage rates (ml/s), including the average and the standard deviation and pressure difference (mmHg) for each tissue annulus diameter and type tested; (ii) one graph for each type of valve which shows leakage rate (ml/s) as a function of back pressure (mmHg), as shown in Figure 4. The test report must contain the information designated in ISO 5840.

(3) Pulsatile flow pressure drop

Provide pulsatile pressure drop, (ΔP), as a function of flow rate, (Q). Equipment and test apparatus must conform to ISO 5840. For mechanical and stented bioprosthetic valves, three valves of each tissue annulus diameter and each type (aortic and mitral), and one aortic (any tissue annulus diameter) and one mitral (any tissue annulus diameter) reference valve must be tested under identical conditions. For stentless tissue valves, the testing must include three stentless valves of each tissue annulus diameter, one 19 mm, and one 31 mm aortic reference valve. For mechanical and stented tissue valves, the testing shall be conducted in a pulse duplicator, as noted in appendix E. For stentless heart valves, the tests shall be conducted in a 4% compliant aortic chamber, unless the device is an intact root prosthesis <u>and</u> it has been shown that device compliance is dominant, as outlined in appendix E, exclusion for intact root.

A minimum of four flow rates will be used to adequately describe the relationship between pressure drop and flow rate over the range of flow rates corresponding to cardiac outputs of 2 to 7 l/min. All tests must be run at a nominal pulse rate (70 beats/min) with systole occupying about 35% ± 2% of the cycle time, and each data point shall be based on (an average of) at least 10 cardiac cycles.

Data must be presented as follows: (i) table of mean pressure drop (mmHg) during forward flow, including the average and standard deviation, and the cardiac output, or mean forward flow, (l/min) for each tissue annulus diameter and type tested; (ii) one graph for each type of valve which shows the average of the mean pressure drop (mmHg) as a function of cardiac output (l/min), as shown in figure 5. (iii) table of average and standard deviation values for (a) mean pressure drop (mmHg), (b) root-mean-square flow rate (Q_{rms}, ml/s), defined as:

$$Q_{rms} = \sqrt{\frac{\sum_{i=1}^{N} Q_i^2(t)}{N}}$$

where $Q_i(t)$ are flow data points in ml/s, i=1 is at start systole and i=N is at end systole, and (c) effective orifice area (EOA) (cm^2), defined as:

$$EOA = \frac{Q_{rms}}{51.6\sqrt{\Delta p}}$$

where Q_{rms} is in ml/sec) and ΔP is in mmHg, for each size and type tested. The 51.6 factor assumes a liquid density of 1.00 g/ml. The EOA may be calculated for each data pair (Q_{rms}, ΔP), or determined by a best fit to the mean pressure drop versus Q_{rms} curve; (iv) one graph for each type of valve which show average of the mean pressure drop as a function of Q_{rms}, as shown in figure 5. The test report must contain the information designated in ISO 5840.

(4) Pulsatile flow regurgitation

Furnish closing, (V_C), leakage, (V_L), and total (V_T) regurgitation volumes as a function of beat rate and cardiac output (see figure 6). Equipment and test apparatus must conform to ISO 5840. For mechanical and stented bioprosthetic valves, three valves of each tissue annulus diameter and each type (aortic and mitral), and one aortic (any tissue annulus diameter) and one mitral (any tissue annulus diameter) reference valve must be tested under identical conditions. For stentless tissue valves, is it necessary to provide the volumes for 3 of the largest valves to be marketed, and for one 31 mm aortic reference valve. For mechanical and stented tissue valves, the testing shall be conducted in a pulse duplicator, as noted in appendix E. For stentless heart valves, the tests shall be conducted using 4% and 16% compliant aortic chambers, unless the device is an intact root prosthesis <u>and</u> it has been shown that device compliance is dominant, as outlined in appendix E, exclusion for intact root. Complete testing of stentless valves in 16% chambers is not required if data can be provided that shows that valve performance is not a function of chamber compliance, as outlined in appendix E, compliance effect validation.

For mechanical and stented bioprostheses, the three volumes must be provided at 3 beat rates with 3 cardiac outputs at each of the beat rates. The range of beat rates is 45 to 120 beats/min, and the range for the cardiac output is 2 to 7 l/min. For stentless valves, only testing at 5 l/min (at three beat rates) is necessary. However, if the measured regurgitation volumes are significantly dependent upon beat rate, then the testing must be conducted at the remaining 2 cardiac outputs.

Data must be presented as follows: (i) table of closing, leakage, and total regurgitation (ml), including average and standard deviation, and cardiac output for each tissue annulus diameter and type tested;
(ii) graphs of closing, leakage, and total regurgitation volumes (ml) versus cardiac output (l/min) at each selected beat rate as illustrated in figure 7. The test report must contain the information designated in ISO 5840.

(5) Flow visualization

Determine the flow characteristics of the valve using flow visualization or turbulence measurement techniques. For these studies, a single-size aortic and a single-size mitral valve must be studied; for stentless valves, a single-size aortic valve must be used. The valve size chosen must be that with which the maximum Reynold's number is associated (usually the smallest). If the test chamber can not accommodate the smallest valve, testing should be conducted on a larger valve using saline. A theoretical comparison of the smallest valve with water and the larger valve with saline should be included. For mechanical and stented bioprosthetic valves, the test must be conducted under pulsatile conditions in appropriately sized aortic and mitral flow chambers, or in a pulse duplicator. For stentless tissue valves, the test shall be conducted using 4% and 16% compliant aortic chambers, unless the device is an intact root prosthesis and it has been shown that device compliance is dominant, as outlined in appendix E, exclusion for intact root. Complete testing of stentless valves in 16% chambers is not required if data can be provided that shows that valve performance is not a function of chamber compliance, as outlined in appendix E, compliance effect validation.

Appropriate physiological conditions would be a heart rate of 70 beats/min, with a cardiac output of 5 to 6 l/min, at a mean aortic pressure of 90 to 100 mmHg. Data must include: a qualitative and/or quantitative assessment of any induced jets, flow stasis, and valvular incompetence which may occur near the valve under test conditions. The use of laser Doppler anemometry must be considered to describe velocity and turbulence profiles generated by the prosthesis. This information can be useful in guiding the optimization of color-Doppler flow-mapping examination during the clinical study. The FDA realizes that this type of evaluation is currently not applicable to stentless tissue valves, as the compliant aortic chambers are not optically clear.

(6) Cavitation potential

Establish the likelihood that cavitation will occur *in vivo*. For mechanical valves, this testing must be conducted on the largest tissue annulus diameter valve. This testing is not required for tissue valves. Because this phenomenon is primarily a function of valve configuration, tests must be performed on production model valves. If cavitation is apt to occur, determine the erosion potential of the valve component materials. Some recommendations for conducting this type of testing can be found in appendix H.

(7) Verification of the Bernoulli Relationship

Since clinical hemodynamic performance will be obtained using Doppler ultrasound, it is necessary to conduct *in vitro* verification to determine whether the coefficient 4 in the relationship $\Delta p = 4(V_d^2 - V_p^2)$ is appropriate. Therefore, determine pressure drop, (ΔP), as a function of flow rate, (Q). For all types of valves, testing must be conducted on one of the largest, one intermediate, and one of the smallest valves, either aortic or mitral. The testing must be conducted in the aortic position of a pulse duplicator. For stentless tissue valves, the test shall be conducted in 4% and 16% compliant aortic chambers, unless the device is an intact root prosthesis and it has been shown that device compliance is dominant, as outlined in appendix E, exclusion for intact root. Complete testing of stentless valves in 16% chambers is not required if data can be provided that shows that valve performance is not a function of chamber compliance, as outlined in appendix E, compliance effect validation.

The distal fluid velocity must be measured with continuous wave Doppler ultrasound directed along the centerline of the aortic chamber to determine the maximum velocity (V_d) in the flow stream. The proximal fluid velocity (V_p) must be measured with pulsed Doppler. The pressure drop must be measured with pressure sensors located at about 30 mm proximal to the valve annulus, and at two distal locations, one at about 30 mm and the second at about 100 mm from the annulus. A minimum of four flow rates must be used to adequately describe the relationship between pressure drop and velocity over the range of flow rates corresponding to cardiac outputs of 2 to 7 l/min. Each data point shall be based on (an average of) at least 10 cardiac cycles. The beat rate, systolic time, type and quantity of ultrasound scattering material used, and the viscosity and density of the blood analogue must be reported.

Data must be presented as follows: (i) table of the calculated coefficient (mmHg s^2/m^2) and the degree of uncertainty at both the 30 mm and 100 mm distal locations, for each tissue annulus diameter tested; (ii) a graph (one for each of the three tissue annulus diameters at the two distal locations for a total of six) which shows mean systolic pressure drop from the pressure transducers versus the mean systolic ($V_d^2-V_p^2$). These must include linear fits to the data which are forced through the coordinate (0,0); (iii) a discussion of the relevance of these results to clinical measurements.

b. Structural Performance

(1) Wear

Provide wear data from accelerated cyclic testing. For all valves, testing should be conducted on three of the largest, medium, and smallest, of each type (aortic and mitral) valve. One equivalent tissue annulus diameter of each type (aortic and mitral) reference valve must be tested at identical conditions. For stentless valves, the reference valve must be a 31 mm stented tissue valve. If the aortic and mitral valves are identical in configuration accept for the sewing ring, then testing only in the mitral position is acceptable. For mechanical and stented tissue valves, the testing must be conducted in accelerated lifetime testers, or pulse duplicators. For stentless heart valves, the tests shall be conducted in the test apparatus with 4% compliant walls.

A minimum peak pressure difference of 90 +20/-0 mmHg must be established across closed aortic valves, and a minimum peak pressure difference of 120 +20/-0 mmHg must be established across closed mitral valves. These pressure differences must be maintained for 95% of the test cycle rates. Furthermore, for all tissue valves, the dP/dt in the system must be determined and reported, in order to characterize the system. Complete opening and closing must be demonstrated for each valve, and for the stentless valves, for each chamber/valve combination used. Mechanical valves will be tested for an equivalent of 15 years (6×10^8 cycles). Tissue valves of all kinds will be tested for an equivalent of five years (2×10^8 cycles). For mechanical valves, all surfaces of each valve must be examined every 40×10^6 cycles for areas of damage (e.g., localized wear, cracks, pits, localized yielding), although disassembly of the valves is not mandatory. All tissue valves must be visually examined every 20×10^6 cycles, or until failure, for any macroscopic damage (e.g., holes, tears, delaminations, fraying, coaptation problems). For stentless valves, in addition to these visual examinations any structural changes in the valve that may impact hemodynamic performance must be assessed. This assessment must be conducted at 0, 60, 140, and 200×10^6 cycles, and testing must be in accordance with sections VI.A.2.a.(3) and VI.A.2.a.(4) of this guidance. For intermediate intervals, hydrodynamic assessments may be limited to pulsatile flow pressure drop measurements at one intermediate cardiac output and pulsatile flow regurgitation measurements at a cardiac output of 5 l/min (at three beat rates) on three valves of each tissue annulus diameter. Measurements of test chamber compliance (with the prosthesis in place) must also be made at these intervals and compared with initial measurements to confirm test condition stability. If remounting the test section for intermediate-interval hydrodynamic testing is problematic, additional valves may be tested and sacrificed at the specified intervals.

This is a comparative test. FDA realizes the limitations of drawing conclusions about clinical performance from an accelerated <u>in vitro</u> test. However, it is possible to develop a valid comparison between the study valve, and a currently marketed valve (control) in terms of performance under the test conditions. Data must be presented as follows: (i) for all valves, observed types and location of damage noted during interim and final visual examinations; (ii) for mechanical valves, damage identified by conducting a complete surface examination, including a scanning electron microscope examination; (iii) for mechanical valves, plot of wear depth versus number of cycles; (iv) for mechanical valves, if failure occurs prior to test termination, a detailed failure analysis; (v) for stentless heart valves, results of intermediate hydrodynamic testing.

(2) Fatigue

Determine the likelihood that any structural components in the device, (e.g., struts, stents, orifices, leaflets) will fail by fatigue within 6 x 10^8 cycles at physiological loading.

(a) Characterization of the material

The materials must be characterized to the extent that all properties necessary for the type of fatigue analysis being performed are appropriately measured. This may include: yield and ultimate strengths; residual stresses resulting from valve fabrication; elastic modulus and Poisson's ratio; stress/life relationship (S/N), including fatigue strength at 6 x 10^8 cycles; fracture toughness (K_{Ic}); and crack growth rates (da/dN). Appropriate dimensional tolerances must be included in the determination of material properties. For example, pyrolytic coating thickness may affect some properties of pyrolytic carbon.

If material(s) properties are to be determined for comparison to calculated stresses in the valve components, the residual stresses resulting from valve component fabrication must be determined and included in the analysis. If actual valve components are tested, residual stresses resulting from valve fabrication need not be explicitly determined, as they will already exist in the item under test. The fatigue characteristics of the material(s) and/or valve components must be conducted at a load ratio at least as severe as that anticipated in vivo, and in an environment representative of physiologic with respect to its effects on fatigue behavior.

Valve components used as test items must be representative of actual components in terms of fabrication methods and defect population.

(b) Stress analysis

A stress analysis of the structural components of the valve shall be performed. This stress analysis must include static stresses (due to pressure differences across the valve), dynamic stresses (or transient stresses which occur as the valve opens and closes), residual stresses (which are present as a result of the manufacturing and forming processes) and which are not included in the test specimens, and stress concentrations (which may be present due to joining or fabrication processes). Two hundred mmHg is a considered a conservative estimate of in vivo loading for a hypertensive patient.

For mechanical and stented bioprosthetic valves, this analysis must be completed on the valve tissue annulus diameter and type (aortic or mitral) which experiences the highest stresses. In many cases, this is the largest diameter valve. However, if component dimensions differ between valve tissue annulus diameters, it is possible that the largest stresses will exist in an intermediate tissue annulus diameter valve. Therefore, while this analysis is required on only one size valve, it will be necessary to establish that the valve size which is being analyzed does indeed experience the highest stresses. For mechanical valves, all components must be considered. For stented bioprosthetic valves, this analysis is required for the stent structure only. For stentless valves, this analysis is not required. The stress analysis must contain the following: (i) measurement of worst case physiological loads or deflections that are applied to the valve components, assuming a continuously hypertensive patient, and justification of the pressure chosen, along with a discussion of the stage in the cardiac cycle at which peak loading occurs (e.g., opening or closing); (ii) A static finite element analysis (FEA), or equivalent, that identifies the stress distribution in the valve components, including the magnitude and location of the maximum static stress. This analysis must specifically establish the effect of in-tolerance variations in dimensions of the components on the magnitude of the maximum stress, and also consider the effect of in-tolerance variation in material's specification; (iii) a determination of the areas and/or components of the valves which are critical structural areas; (iv) the addition of the residual stresses which are present from manufacturing and/or production to the static stresses; (v) for mechanical valves, the determination of the magnitude and locations of the transient loads present at valve opening or closing, whichever is worse. These stresses must be added to the static and residual stresses. Additional information on the determination of these transient stresses can be found in appendix I.

(c) Fatigue lifetime determination

Complete a conservative fatigue analysis to predict the minimum safe, structural fatigue life of the device. This analysis can be based on either traditional stress/life (a.k.a fatigue/reliability) principles (S/N), <u>or</u> damage-tolerance principles (fracture mechanics). An evaluation of the effects of all forming, joining, and other manufacturing processes of each component on the design life of the valve must also be included.

It is left to the discretion of the manufacturer to determine whether an S/N or damage-tolerance analysis is most appropriate for the specific material and valve design. However, classical S/N analysis is not encouraged for mechanical valves. The S/N analysis is conducted on "laboratory perfect" specimens (i.e., those which presumably do not contain defects). Therefore, the total life of the components, as determined by this type of testing, includes the crack initiation stages. Under these conditions, crack propagation can not be specifically segregated out for analysis. However, the basic premise of the damage-tolerance approach is that all components contain inherent flaws. By using test samples with pre-existing, well-defined flaws, the testing provides meaningful information about how defects will propagate. This intrinsically conservative approach has been used widely in critical applications where catastrophic failure will result in loss of life[6].

S/N

An endurance limit, as classically defined, does not exist for most materials in the physiological environment. Most materials do not contain an endurance limit, even under controlled environmental conditions (dry air). However, in corrosive environments S/N data show a continually sloping curve[7]. Therefore, the use of literature S/N data is not acceptable, unless it can be shown that (i) the samples used in the testing have the same microstructure, compositions, etc.; (ii) the R ratio and mean stress used in the testing are consistent with or more conservative than physiological loading; (iii) the fatigue resistance of the material is not effected by environment, or the environment used in the testing is representative of physiological conditions; (iv) the data presented is representative of an appropriate survival rate (as opposed to the median survival normally provided).

Nonetheless, it may not be necessary that the exact magnitude of the material or structural fatigue strength at 6×10^8 cycles be determined. It will be necessary that a minimum of 90% survival with 95% confidence, in an appropriate environment, be established. If appropriate testing demonstrates this level of survival at stresses exceeding the peak in vivo stresses calculated as per the preceding section, times an appropriate safety factor, then acceptable survival has been demonstrated. If S/N analysis is chosen, it is left to the manufacturer to determine an appropriate defect size which must be detected, and an appropriate method for identifying these defects, or show that the samples tested are representative of valve components.

If material-property specimens are tested, the safety factor is defined as the lowest test stress that results in the required survival divided by the calculated peak in vivo stress. If valves or valve components are tested, the safety factor is defined as the lowest test load (or pressure) that results in the required survival divided by the dynamic load caused by a 200 mmhg or greater peak systolic pressure. A minimum safety factor is not specified here. The safety factor must be reported and justified by the manufacturer, and will be evaluated in the context of other conservative or non-conservative assumptions made in the analysis.

If the manufacturer chooses to test samples, or sections of heart valves, instead of the entire valve, it is necessary that the test apparatus produces stresses that mimic in vivo stress conditions, not (stent) deflections. The frequency of the testing must be appropriate.

Damage tolerance analysis

Determine the following: (i) the crack growth rates resulting from both cyclic loading (which produces fatigue) and sustained loading in a corrosive environment (which produces environmentally-assisted static fatigue or corrosion fatigue) must be determined; (ii) maximum allowable initial flaw size which will not propagate to failure in 6 X 10^8 cycles; (iii) calculation of the minimum assured lifetime in a continuously hypertensive patient, (iv) the appropriate statistical requirements have been met for validating quality control processes in terms of detection, based on the expected population of defects. This analysis should also include a sensitivity analysis that reveals how various assumptions and parameters impact upon lifetime. The application of ASTM testing procedures to low-toughness material has been described in the literature[8].

If sub-critical crack-growth rates under sustained (non-cyclic) loading conditions, i.e. stress corrosion cracking rates, exceed those measured under cyclic loading, then life predictions computations must be performed with the stress corrosion rates.

If the components of the valve are composite in nature, this fact must be taken into consideration. Furthermore, for some materials, the existence of a threshold stress intensity has not been established. It is the responsibility of the manufacturer to establish that such a threshold exists for the material used to fabricate the device. Alternatively, it is acceptable to assume that the threshold does not exist in the analysis. Furthermore, consideration must be made as to whether the "small crack effect" is important.

Fatigue/manufacturing

Discuss the effect of the following manufacturing issues, as applicable, on the anticipated life of the valve: (i) the presence of voids or impurities in as-received materials, the maximum allowable size, percentage or concentration of these discontinuities, and the methodology of assuring that these limits are not exceeded; (ii) the presence of voids or impurities that are introduced during a manufacturing process, the maximum allowable size, percentage or concentration of these discontinuities, and the methodology of assuring that these limits are not exceeded; (iii) for those instances where a the maximum allowable flaw size has been calculated, the methodology of assuring that flaws in excess of this size are not present in the valve. It must be shown that the probability of accurate detection for flaws using a proof test of a non-destructive crack-detection procedure is at least 99% with 95% confidence; and (iv) the effect of the dimensional changes imposed on the valve components during assembly, and a determination of the resulting stresses in the valve due to this process. A consideration of low-cycle fatigue may be appropriate. This analysis must also establish the effect of in-tolerance variations in clearances on the magnitude of deflection required to assemble the valve.

(3) Dynamic failure mode

Provide pulsatile test data that indicates the qualitative and/or quantitative assessment of the failure modes and high stress areas in the valve. To some extent the results of this can be used to validate a finite stress analysis of the components. For mechanical and stented bioprosthesis valves, a selection of valves which have survived the wear testing must be subjected to additional testing to determine the mode in which the valve will fail under accelerated cycling. This testing is not required on stentless tissue valves. Data must be presented as follows: details of failure modes observed, and the location of the failures. FDA recognizes that it is difficult to correlate failure modes observed under these testing conditions to those observed in vivo, due to artifactual wear that occurs in the in vitro testing. However, if correlations can be drawn between test results and physiological conditions, these results must be discussed.

(4) Sewing ring integrity

Determine the loads required to produce sewing ring dehiscence, as well as the ultimate failure mode of the sewing ring. If the sewing ring has a seam, the pull strength of the seam must also be determined. For all valves, three valves of each tissue annulus diameter and each type (aortic and mitral) must be tested. The data must be presented as follows: (i) maximum loads which can be supported by the valve, and a comparison to physiological loading (including safety factors); (ii) description of the observed failure modes, e.g., tearing of the cloths, separation from the orifice, etc.; (iii) sewing ring seam pull strength.

(5) Design specific testing

The description of the tests in this section are not all inclusive. This listing simply provides a representative sample of the types of testing which are design specific. Each manufacturer is responsible for determining the types of structural testing which would be appropriate for the valve design under consideration.

(a) creep of stents (for stented bioprosthetic valves)

Determine the creep of the structural components (e.g., stents) under cyclic loading. Appropriate environmental conditions must be utilized in the testing, as well as a loading of at least two times physiological. The frequency and length of the testing is left to the discretion of the manufacturer, but the selection must be justified.

(b) deflection of stents (for stented bioprosthetic valves)

Determine the deflection of the stents assuming a continuously hypertensive patient. If each stent post (with the leaflet attached) does not deflect symmetrically under the loading, the deflection of each stent post must be measured individually. These measurements must be collected on six valves. The valve tissue annulus diameter and type chosen must be that valve which experiences the largest stress. The highest commissure tip deflection from this sampling must be used in the stress analysis. Maximum in-tolerance variations in stent cross-sectional area must be considered.

(c) ball ejection force (for ball-and-cage mechanical valves)

For the largest valve of each type (aortic or mitral), or for the worst case, determine the pressure required to force the ball through the struts and through the orifice.

(d) leaflet impingement force (for bileaflet valves)

For the largest valve of each type, determine the maximum radial compressive force which can be applied to the valve housing along the centerline where the leaflets meet before the housing distorts sufficiently to produce leaflet impingement or impeded motion.

(e) leaflet escape force (for bileaflet valves)

For the largest valve of each type, determine the maximum radial compressive force which can be applied to the valve housing perpendicular to the centerline where the leaflets meet before the housing distorts sufficiently to allow leaflet escape.

(f) absorption and adsorption (in polymeric materials)

The effect of biological absorption and adsorption (of waters, protein, lipids, etc.) on the dimensions and mechanical properties or critical components must be determined. The time dependence of any changes must also be identified (e.g., modulus decreases 10% initially, and the stabilizes at a given value).

(g) corrosion (for metallic valves)

The corrosion resistance of all metallic materials, under stress (if appropriate) must be determined in a physiological environment. If cyclic loading is present, tests must be conducted under the same type of loading at a frequency which will not mask any possible forms of localized attack. Final forming methods, such as welding, must be considered. It is not acceptable to evaluate the effects of localized attack (such as pitting) using weight loss methods, unless it can be established that the sensitivity of the experimental technique is sufficient to identify any attack which is occurring. It may be possible to justify the use of a material based on historical use in prosthetic heart valves, but it is necessary to discuss the potential reactions due to the contacting of different materials.

3. Shelf life

A description of the protocol for shelf life studies (along with the justification for the sample size used) and the results of the studies must be included. Shelf-life data, as specified in the labeling, must be based on the ability of both the replacement heart valve and the package to maintain their integrity out to the claimed shelf life. While real-time aging is not required, accelerated aging studies must include the effects of temperature, humidity, pressure and light exposure, as well as shipping and handling (dropping and vibrating). It is not sufficient to simply perform sterility testing after storing the assemblies. After subjecting the assemblies to the simulated or real-time environment, the devices must be tested for sterility and functionality. For tissue valves, the shrink temperature, moisture content, collagen content, and other appropriate tests must be performed. Additionally, the storage solution must be checked for percentage of remaining preservative ingredients (glutaraldehyde, ethanol, etc.) and for volume remaining, leakage, seal integrity, etc. For mechanical valves, the choice of appropriate functionality tests is left to the manufacturer.

In validating the package shelf life, it is acceptable to use simulated devices, as long as the geometry and mass approximate that of the actual clinical device. It is not appropriate to test empty packages after a microbial challenge. The simulated devices must also undergo shipment, handling, and storage conditions. A variety of standard and military specifications are available in developing simulated conditions. These documents are summarized in a bibliography[9]. For those products which are tissue based, the use of a temperature sensor is necessary to ensure that the valve has not been exposed to temperature extremes which may adversely affect the tissue. The accuracy of the temperature sensor must also be validated.

Current policy regarding extension of shelf life indicates that if an approved protocol is in place, extensions in shelf life can be reported to the FDA in the annual report for the heart valve.

4. Preclinical Animal Studies

Animal studies should be conducted in accordance with the appropriate sections of ISO 10993-2. A fundamental component of establishing replacement heart valve safety involves the in vivo evaluation of the valve in an appropriate animal model. It is recommended that the pre-clinical animal safety studies of a prosthesis include: acute evaluation of orthotopic hemodynamic performance; chronic assessment of hemodynamic performance and valve related pathology in either an orthotopic or non-orthotopic position; and, chronic evaluation of anticalcification treatments of tissue valves, if indicated, in either an orthotopic or non-orthotopic position.

Mechanical and bioprosthetic valves are routinely evaluated by means of orthotopic valve replacement in an appropriate animal model. However, chronic (20 week) aortic valve replacement using a stentless bioprosthesis may be difficult due to limitations of existing animal models. Preliminary studies suggest that in the aortic position, marked wound healing occurs which severely limits the evaluation of stentless valve performance. Although chronic orthotopic assessment of stentless bioprosthetic valve safety and efficacy would be optimal, the feasibility of non-orthotopic implantation of stentless heart valves for a period of 20 weeks in juvenile sheep is being investigated.

a. Acute Studies

Acute (e.g., intraoperative) hemodynamic studies must be designed to evaluate the orthotopic hemodynamic performance of a replacement heart valve. These studies are required only if the chronic studies will include animals with a valve implanted in a non-orthotopic location. Acute data must be obtained from three orthotopic valve replacements in an appropriate animal model (e.g., bovine, ovine, canine) over a range of cardiac outputs (equal to or greater than 3 l/min). The following information must be provided: (i) ease of handling and surgical implantation (e.g., valve packaging, valve holders, methods used to determine appropriate heart valve tissue annulus diameter); (ii) mean and peak pressure difference across the valve; (iii) effective orifice area; (iv) assessment of leaflet motion; and, (v) the presence of stenosis and/or regurgitation.

b. Chronic Studies

A minimum of six animals must survive an implantation period of at least 20 weeks. It is strongly recommended that at least 2 additional animals be implanted with a similar valve with a known clinical experience to serve as concurrent controls. Animals with infected prosthetic valves must be identified and reported, but may be excluded from the population used to assess prosthetic valve performance. For mechanical and stented porcine valves, the valve must be implanted in an **orthotopic** position. For stentless valves, chronic studies must be conducted in an appropriate animal model in which the stentless valve is implanted in either an **orthotopic or non-orthotopic** site. Acute hemodynamic performance data (e.g., intraoperative), as described above, must be submitted to validate the appropriateness of the non-orthotopic implantation site.

(1) Chronic Studies on animals surviving less than 20 weeks

The following information must be included:
(i) Justification of the animal model. For biological valves, this includes a demonstration that prosthetic valvular calcification occurs in the species and age of animal selected for the study. Use of literature references may be appropriate for validating the model;
(ii) Pre-operative evaluation, including verification of the age of the animals (i.e., determination of age by dental eruption time and morphological changes of dental tables);
(iii) Description of the surgical procedures and the ease of handling and surgical implantation (e.g., valve packaging, valve holders, methods used to determine appropriate heart valve tissue annulus diameter), plus post-operative care, anticoagulation regime and animal housing;
(iv) Length of implantation;
(v) Cause of death. If valve related, identity of the cause (e.g., valve failure, primary leaflet disruption, endocarditis) with a supporting pathology report;
(vi) Laboratory studies, including red blood count (RBC), white blood count (WBC), hematocrit, free hemoglobin, serum lactate dehydrogenase (SLDH), haptoglobin, and reticulocytes and platelet count, serum calcium and phosphorous, and leaflet calcium and phosphate (tissue and polymeric leaflet valves);
(vii) Systemic pathology studies including gross examination, organ weights, and histopathology of heart, spleen, liver and kidney;
(viii)Explanted valve analysis, as outlined in appendix J, including histopathologic studies of specific lesions previously identified.

(2) Chronic studies on animals surviving more than 20 weeks

The following information must be included:
(i) Justification of the animal model, as described above;
(ii) Pre-operative evaluation, including verification of the age of the animals (i.e., determination of age by dental eruption time and morphological changes of dental tables);
(iii)Description of the surgical procedures and the ease of

handling and surgical implantation (e.g., valve packaging, valve holders, methods used to determine appropriate heart valve tissue annulus diameter), plus post-operative care, anticoagulation regime and animal housing;
(iv) Laboratory studies, including red blood count (RBC), white blood count (WBC), hematocrit, free hemoglobin, serum lactate dehydrogenase (SLDH), haptoglobin, and reticulocytes and platelet count, serum calcium and phosphorous, and leaflet calcium and phosphate (tissue and polymeric leaflet valves);
(v) Hemodynamic studies over a range of cardiac outputs (equal to or greater than 3 l/min) including peak and mean pressure differences across the valve, and effective orifice area. Instrumentation and test methods must be included;
(vi) Cineangiographic/ventriculogram studies evaluating mechanical occluder motion and valvular regurgitation;
(vii) In situ photographs of the replacement valve inflow and outflow regions and valve surfaces;
(viii) Systemic pathology studies including gross examination, organ weights, and histopathology of heart, spleen, liver an kidney;
(ix) Explanted valve analysis, as outlined in appendix J, including evaluation of biomaterials wear and deformation, healing of cuffs at the tissue annulus, and histopathologic studies of specific lesions previously identified.

c. Anticalcification Treatment Studies

For bioprosthetic valves, anticalcification-treatment studies must be designed to evaluate the effectiveness of proprietary treatments designed to mitigate calcification. These studies are required only if the tissue is treated with an anticalcification treatment. The effectiveness of the treatment must be demonstrated in an appropriate chronic animal model. Validation of the animal model (species, age, implantation site, animal housing) must include the demonstration of bioprosthetic valve calcification. It may be possible to validate the use of a non-orthotopic implantation site for the purpose of collecting data. These studies must include a quantitative comparison of the extent of calcification in a treated valve versus an untreated control valve of identical design and fabrication. A statistically significant difference between treated and control valves should be demonstrated.

Animal data alone are not considered sufficient to support claims of anticalcification treatment efficacy. Long-term clinical data will be required to substantiate labeling claims.

5. Accessories

Accessories for heart valves are class II devices which may be found substantially equivalent to accessories currently available. However, an accessory to a class III device (such as a heart valve) can not be found substantially equivalent until the class III device itself has been approved for marketing. Therefore, it would be necessary to obtain PMA approval for a heart valve before submitting a 510(k) for the accessories to be used while implanting the heart valve. FDA acknowledges that this may produce a safety problem if the valve is approved, and the accessories are not, as the surgeons would be forced to utilize accessories not designed for use with that particular valve. Therefore, it is recommended that the accessories be included in the PMA for the valve itself; marketing approval for the valve and its accessories would be granted concurrently. The following information must be provided for accessories to heart valves: (i) the intended use(s); (ii) labeling and instructions for use; (iii) the sizes in which the accessory(ies) is available; (iv) the type of valve (aortic, mitral, all) with which the accessory(ies) should be used; (v) material(s) from which they are fabricated; (vi) description of manufacturing methods; (vii) description of biocompatibility testing or historical use of the material(s); (viii) drawing(s), with dimensions; (ix) the number of times the device(s) can be used; (x) if the device(s) is supplied sterile or non sterile; (xi) how many times the device(s) can be resterilized, and if the recommended number of resterilizations is based on testing or historical data; (xii) how the device(s) is supplied (e.g., as a kit, individually, etc.); (xiii) packaging. If the device(s) is supplied non sterile, the instructions for use must contains recommended sterilization cycles. These cycles must be validated.

B. Clinical Investigations

1. Regulatory Issues

The PMA application must contain a copy of the protocol used to collect the clinical data (as indicated in the PMA checklist). Although permission to conduct a clinical study is not directly linked to the review of a PMA, the manufacturer should realize that the design of the clinical study must be such that appropriate data, which shows that the device is safe and effective, are collected.

In accordance with CFR 814.15, clinical data collected at foreign centers under an investigational device exemption (IDE), must comply with CFR 812. Furthermore, clinical data collected at foreign centers after November 19, 1986, but not under an IDE, must have been collected in conformance with the "Declaration of Helsinki," or the laws and regulations of the country in which the research is conducted, whichever accords greater protection to the human subject. The PMA application must indicate, for each foreign center, if the data were collected in accordance with the IDE, the "Declaration of Helsinki", or the country standards. If the standards of the country were used, a comparison between those standards and the "Declaration of Helsinki" must be included. A copy of the "Declaration of Helsinki" can be found in the Premarket Approval Manual.

If the application is based solely on foreign data, in addition to demonstrating that the rights, safety and welfare of human subjects have not been violated, it must be shown that the foreign data are: applicable to the United States population for which the device is intended, that the medical practices in the foreign countries are comparable to those used in the United States, and that the studies were conducted by clinical investigators of recognized competence. It may be possible to support the claim of comparability of patient populations (foreign versus U.S.) using literature citations. The establishment of comparability must be based on not only demographic comparisons (age, implant position, sex, concomitant surgery), but the criteria used for selecting patients for valve replacement.

Primary centers are all centers implanting the valve in the United States, and all foreign centers which are listed in the IDE. All patients at the primary centers must be completely accounted for in the clinical data. It is expected that each patient entered into the study will be followed according to the study protocol, and that any patient not willing or able to fully participate should not be entered. It must be understood by the patients that follow-up visits will continue until PMA approval is granted, or the study is terminated. For most patients, therefore, the follow-up period may be significantly longer than (the minimum required) one year.

Clinical data included in any application must be current to within six months of the date of submission.

2. Clinical Utility

One of the provisions of the Safe Medical Devices Act (1990) is that the information included in the PMA application must establish that the device has clinical utility. Therefore, the application must include a general discussion about the clinical utility of replacement heart valves.

3. Study design

The clinical study must establish that the device is both safe and effective, as compared to currently marketed devices in patient requiring replacement heart valves. It is possible to achieve this goal using hypothesis testing to compare the results of a observational study against a set of Objective Performance Criteria (OPC) which have been previously established by the FDA. A discussion of the basis for the OPCs in located in the background section of this document, and the OPCs can be found in